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Surround Inhibition in the Motor System

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Abstract

Surround inhibition is a physiological mechanism to focus neuronal activity in the central nervous system. This so-called center-surround organization is well-known in sensory systems, where central signals are facilitated and eccentric signals are inhibited in order to sharpen the contrast between them. There is evidence that this mechanism is relevant for skilled motor behaviour, and it is deficient, for example, in the affected primary motor cortex of patients with focal hand dystonia (FHD). While it is still not fully elucidated how surround inhibition is generated in healthy subjects, the process is enhanced with handedness and task difficulty indicating that it may be an important mechanism for the performance of individuated finger movements. In FHD, where involuntary over-activation of muscles interferes with precise finger movements, a loss of intracortical inhibition likely contributes to the loss of surround inhibition. Several intracortical inhibitory networks are modulated differently in FHD compared to healthy subjects, and these may contribute to the loss of surround inhibition. Surround inhibition can be observed and assessed in the primary motor cortex. It remains unclear, however, if the effects are created in the cortex or if they are derived from, or supported by, motor signals that come from the basal ganglia.

Keywords

Human; transcranial magnetic stimulation; contrast

Introduction: Sensory systems

In the central nervous system, one physiological mechanism to select neuronal responses and to focus neural activity is surround inhibition or lateral inhibition (these terms will be used synonymously). In sensory systems, there is a well-known center-surround organization which is thought to help sharpen sensory perceptions. This phenomenon was first described in the visual system and is thought to improve spatial and temporal discrimination of various sensory inputs in the visual system (Blakemore et al. 1970). In the retina, cells are excited by light that falls into the center of their receptive field, whereas light falling into the periphery has an inhibitory effect onto the same cell (Angelucci et al.

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2002). Thereby the contrast between the two signals is enhanced. Surround inhibition operates also in the somatosensory system. A simple demonstration of surround inhibition in the human somatosensory system is the mutual inhibition of the somatosensory evoked potential (SEP) amplitude from the median and ulnar nerves (Tinazzi et al. 2000). Surround inhibition can also be demonstrated in a sensorimotor interaction. For example, the inhibitory effect of second finger stimulation on a motor evoked potential (MEP) was reduced by stimulating the first and third fingers at the same time as the second (Tamburin et al. 2005).

A similar phenomenon of surround or lateral inhibition can be observed on the cortical level in models of focal epilepsy, in which autoradiography with [14C]deoxyglucose was used to study the architectural pattern of glucose utilization in the motor cortex of rats during focal penicillin seizures (Collins 1978). Results from this study show that besides the 2-or 3-fold increase of glucose metabolism in the center of the epileptic focus, in cortex surrounding the epileptic focus there was an increase in synaptic inhibition resulting in a normal or slight decrease in autoradiographic density (Collins 1978). Such findings likely indicate a general pattern of cellular connectivity intrinsic to cortical organization.

Motor system

Concerning the motor system, there is evidence that surround inhibition, mediated through GABAergic transmission, could aid the selective execution of desired movements in humans (Mink 1996; Ziemann et al. 1996; Hallett 2003). Single finger movements are never completely isolated contractions of one muscle, but need simultaneous control of the entire hand and forearm involving contraction of many muscles acting on different fingers and joints (Schieber, 1991). For example, when human subjects are asked to exert maximal voluntary force with one digit, the forces produced unintentionally by fingers not explicitly involved in the voluntary task (termed “force enslaving”) can reach amplitudes up to 50% of the force produced by the instructed digit (Zatsiorsky et al. 2000). This may be, in part, due to biomechanical constraints of the hand, but since force enslaving seems to be similar regardless of the muscle groups involved, it is more likely that the whole motion pattern is generated in central nervous system (Zatsiorsky et al. 2000). During motor activation, active muscles show increased excitability while neighboring muscles are inhibited (Sohn and Hallett 2004b).

Animal models provide evidence of the crucial role that local GABAergic circuits have on motor output. In cats, GABA-antagonist drugs cause a merging of motor hotspots of adjacent muscles when they are applied to the motor cortex (Schneider et al. 2002). In the primate motor cortex, which is probably most closely related to the human motor cortex, the cortico-spinal cells projecting to one specific muscle are distributed over a relatively wide area in the cortical hand area, and a single cell is connected to several muscles (Landgren et al. 1962; Andersen et al. 1975). Single M1 neurons discharge in relation to multiple finger and wrist movements (Schieber et al. 1993). Partial inactivation of M1, for example by muscimol injections to specific parts of M1, does not lead to somatotopically organized motor impairment (Schieber et al. 1998). In primates, intracortical inter-connections between distant sites projecting to the same muscle can be assessed by using

microelectrodes in the hand area of the motor cortex (Baker et al. 1998). Stimulation can be applied using single or paired pulses of the same intensity and different inter-stimulus intervals to different areas in M1 or to the pyramidal tract and be recorded from pyramidal tract neurons. Simultaneous stimulation of two different sites (distance 1.5–2.0 mm) induces spatial facilitation comparable to the amount of cortical stimulation on one site paired with pyramidal tract stimulation (Baker et al. 1998). Therefore it was concluded that this was rather a spinal summation effect than a cortical interaction. Moreover, stimulation of two cortical sites that are 2.0mm apart with an inter-stimulus interval of 10–20ms does not change the MEP size compared to stimulation of one site alone. In contrast, stimulation of the same site twice with a delay of 10–20ms induces an over-additive enhancement suggesting that this reflects differences in the summation of powerful interconnections in response to local versus remote stimulation (Baker et al. 1998). These findings suggest that horizontal intracortical axon collaterals that interconnect the entire M1 hand representation area (Huntley and Jones, 1991) may be involved in the coordination of patterns of motor output to multiple muscles.

The role of the basal ganglia

The idea that surround inhibition may be a relevant mechanism to aid the selective execution of desired movements by inhibiting undesired and eventually interfering motions goes at least back to the work of Denny Brown (Denny-Brown and Yanagisawa 1967). His clinical observations of the effects of basal ganglia lesions, such as loss of focusing, switching movement patterns, bradykinesia and context-specific facilitation of movement led them to attribute these functions to the basal ganglia circuits (Hallett and Khoshbin 1980).

In accord with these thoughts, Mink summarized previous experiments and observations in a influential review in 1996 and proposed an anatomical hypothesis of the generation of surround inhibition (1996). Also derived from clinical features observed in patients with basal ganglia disorders, such as slowness of movement, rigidity, involuntary postures and uncontrollable movements, and animal models, he suggested that the inhibitory output of the basal ganglia may act selectively to inhibit competing motor mechanisms in order to prevent them from interfering with voluntary movements that are generated by other structures in the central nervous system (Mink 1996).

The striatum receives input from nearly all of cerebral cortex such that several functionally related cortical areas project to overlapping striatal zones and that an individual cortical area projects to several striatal zones. Cortical areas that are not functionally related project to separate zones of the striatum, although there may be some striatal neurons that receive input from more than one adjacent zone (Mink 1996). In the striatum, there are multiple mechanisms that integrate inputs and focus the output. The multiply convergent and divergent pattern of the cortico-striatal projections provides an anatomical substrate in the striatum for the integration of information from several different areas of cerebral cortex (Graybiel et al., 1994).

Output from the striatum is inhibitory and projects to the basal ganglia output nuclei globus pallidus internus (GPi) and substantia nigra pars reticulate (SNpr). The striatum also sends

an inhibitory projection to globus pallidus externus (GPe) which, in turn, inhibits the subthalamic nucleus (STN) and GPi. This so-called “indirect” pathway from striatum through GPe (and STN) could act in opposition to the “direct” pathway and result in further focusing of the information flow from striatum to GPi (Mink 1996; see Fig. 1). An individual GPi neuron sends output via thalamus to just one area of cortex (Hoover and Strick, 1993). GPi neurons that influence the motor cortex are adjacent to, but separate from, those that influence the premotor cortex. This arrangement is evidence for functionally segregated parallel outputs of the basal ganglia (Alexander et al., 1986; Hoover and Strick, 1993). It appears likely that in making a movement, the total motor control signal is both an excitatory command for the desired movement and an inhibitory command for undesired movements (Mink, 1996; Sohn and Hallett, 2004b; see Fig. 1). Besides projections to some areas of the frontal lobe (Alexander et al. 1986) and the brainstem (Parent and De Bellefeuille, 1982), the majority of the basal ganglia output goes via thalamus to motor cortical areas (Nauta and Mehler, 1966) indicating the important role of the basal ganglia circuits on motor control. A number of investigators have felt that in patients with focal hand dystonia (FHD) there is an imbalance in the direct and indirect pathways so that the direct pathway is relatively overactive or, saying it the other way, that the indirect pathway is relatively underactive (Hallett, 2004; Hallett, 2006). The direct pathway helps command the desired movement, while the indirect pathway inhibits unwanted movements (Mink, 1996). The postulated imbalance in FHD could lead to excessive movement and, in particular, a loss of surround inhibition.

The role of primary motor cortex (M1)

In humans, surround inhibition can be assessed using transcranial magnetic stimulation (TMS). A facilitation of the desired movement and inhibition of the neighboring, uninvolved movements can be observed in the primary motor cortex (Sohn and Hallett 2004b). For example, if a certain force is exerted by the index finger, MEPs recorded from FDI, as a synergistic muscle in the task, are facilitated (see Figure 2), while MEP amplitudes in APB, which is a surrounding muscle and not involved in the task, are reduced (see Figure 3). Surround inhibition is a functional inhibition shaped in time and space (Hallett 2006; Beck et al. 2008). The whole phenomenon of surround inhibition is restricted to the movement initiation phase (just before and during the first phase of EMG-onset), but absent during the tonic phase of the contraction, which means the maintenance of a contraction for a few seconds (Beck et al. 2008).

The brief initial facilitation on the spinal level, that is observed during movement initiation, is called the Jendrassik effect. It can be tested using H-reflexes and is not spatially selective (Zehr and Stein 1999). Its relevance for motor performance is not completely understood, but it may help rapid movement generation, since, in contrast to other neurons of the central nervous system, spinal alpha-motoneurons do not show spontaneous activity. Therefore, surround inhibition may help to select desired movements by a selective antagonism of the spinal facilitation (Beck et al. 2008). During the maintenance phase or tonic phase of the contraction, there is no more increase of spinal excitability and therefore surround inhibition may no longer be necessary (Beck et al. 2008). Results from this study suggest a supra-spinal generation of surround inhibition.

Moreover, surround inhibition has been shown to depend on certain characteristics of the task performed. While surround inhibition is more pronounced in the dominant hemisphere of right handed subjects than in the non-dominant hemisphere (Shin et al., 2009), it is also stronger with low force levels, such as 10% of the maximum force, and disappears when more than 40% of the maximum force is exerted (Beck et al. 2009b). Surround inhibition starts earlier with increasing task difficulty (Beck and Hallett, 2010) suggesting that attention may play a role in its generation, since increased attention enhances intracortical inhibition (Liepert et al. 1998; Conte et al. 2007). These findings may indicate a cortical origin or at least cortical modulation of surround inhibition.

The role of M1 and other cortical motor areas projecting to M1 for the generation of surround inhibition can be assessed non-invasively using TMS. Applying a paired pulse TMS paradigm, in which a sub-threshold TMS pulse precedes a supra-threshold test pulse leading to a decrease in the amplitude of the motor evoked potential, inhibition from local intra-motor cortical interneurons can be assessed (Kujirai et al. 1993). The so-called short intracortical inhibition (SICI) has been reported to contribute to surround inhibition in healthy subjects (Stinear and Byblow, 2004). In contrast, two other studies could not confirm this finding even when similar muscles were tested (Sohn and Hallett 2004b; Beck et al. 2008).

Other studies of inhibitory projections onto M1 in healthy subjects show that there is a general reduction of inhibition in different cortico-cortical circuits during movement initiation: Long intracortical inhibition (LICI; Sohn and Hallett, 2004b), short afferent inhibition (SAI; Richardson et al. 2007), long afferent inhibition (LAI, Pirio Richardson et al. 2009) and inter-hemispheric inhibition (Beck et al. 2009a) are decreased just before or during the first phase of movement. All these mechanisms, like the Jendrassik effect, operate against the surround inhibition mechanism.

Focal hand dystonia

Another strategy to gain better insight into the mechanisms involved in the physiology of surround inhibition is to compare healthy volunteers with patients with FHD. In the primary motor cortex, FHD patients show deficient surround inhibition during movement initiation (Sohn and Hallett 2004b; Beck et al. 2008; see Fig. 3). Impairment of high-precision motor tasks associated with unwanted muscle spasms, as when playing the piano or writing, is the principal clinical feature of FHD. The comparison of healthy volunteers with FHD patients may therefore be helpful to gain further insight of the underlying mechanism of surround inhibition.

As pointed out before, local inhibitory interneurons in M1 may contribute to generate surround inhibition and can be tested by using a well-established paired pulse TMS paradigm (Kujirai et al. 1993). If this paradigm is used during different phases of the movement, the intensity for the conditioning TMS pulse is constant, while the test pulse size is adjusted for each phase. In FHD, there is evidence for a loss of SICI during movement initiation in a reaction time task (Beck et al. 2008; see Fig. 4). This finding supports the idea that the local inhibitory interneurons play a key role in the generation of surround inhibition.

The inhibitory projection onto M1 from the dorsal-premotor cortex (PMd) was enhanced in the resting state when compared to healthy subjects and the inhibition decreased during movement in patients with FHD, while no change in this influence was seen in normal subjects (Beck et al. 2009c). Hence, this mechanism also might contribute to the loss of surround inhibition in FHD.

Another characteristic clinical feature of FHD is called mirror dystonia. This term describes the induction of an involuntary posture during motor performance of the unaffected hand (Jedynak et al. 2001). If the unaffected hand imitates the specific dystonia-inducing movement of the affected hand, the motor overflow occurs in the resting, affected hand. This phenomenon can be observed in about half of the patients with FHD (Jedynak et al. 2001) suggesting that the contralateral, “healthy” M1 may be important for surround inhibition and its deficiency in FHD. Using another paired pulse TMS paradigm, inhibition from the contralateral M1, which is mediated via excitatory transcallosal fibers and projects onto the intra-motor-cortical inhibitory network, can be assessed, the so-called interhemispheric inhibition (IHI) (Ferbert et al. 1992). IHI is differentially modulated before movement onset between the dominant and non-dominant hand, in that it is decreased towards the dominant M1 prior to unilateral hand movement in healthy volunteers (Murase et al. 2004; Duque et al. 2007). A recent study comparing healthy volunteers with FHD patients with and without mirror dystonia showed that IHI between surrounding muscles is specifically reduced before EMG onset in the group of patients with mirror dystonia, but not in the patient group without mirror dystonia. This indicates that a loss of IHI may be a underlying cause for the clinical phenomenon, but not a general deficit in FHD (Beck et al. 2009a), furthermore IHI was not enhanced, when surround inhibition was present in the healthy subjects making it unlikely that this interaction plays a role in its generation (Beck et al. 2009a).

There is also evidence in FHD for loss of inhibition in sensory function. For example, patients have less inhibitory influence of median and ulnar nerve stimulation on their respective SEPs (Tinazzi et al. 2000). It is likely that the disturbed somatotopy in the primary sensory cortex (Bara-Jimenez et al. 1998; Tamburin et al. 2002) is a result of defective inhibition as well.

Another electrophysiological finding in FHD patients that may be related to the loss of surround inhibition, is increased cortical plasticity (Quartarone et al. 2003; see Fig. 5). Cortical plasticity can be induced using a paradigm called paired associative stimulation (PAS), in which a peripheral electrical stimulus is timed to coincide on the cortical level with the transcranial magnetic pulse over the scalp and thereby leads to increased excitability that is though to be due to mechanisms like long term potentiation (Stefan et al. 2000). In FHD, the induced plasticity assessed as increase in MEP amplitude after the intervention is stronger and less focal compared to healthy subjects (Quartarone et al. 2003). For example, if the plasticity is focused on the APB by stimulating the median nerve, there are abnormal increases of motor cortical excitability in ulnar nerve muscles, FDI (Quartarone et al. 2003; see Fig. 5) and ADM (Weise et al., 2006). This is another abnormality probably due to a loss of surround inhibition and somatotopy in the sensorimotor cortex,

In Parkinson's Disease (PD) deficient surround inhibition has also been demonstrated, even before clinical manifestation (Shin et al. 2007). In contrast to healthy volunteers, PD patients show a facilitation of MEP amplitude in the surrounding muscle during motor activation (Shin et al. 2007). While there is some overflow of voluntary movement in PD and overt dystonia can be seen, dystonic movements are not a marked clinical feature in PD. Since with these TMS studies, there is a similar pattern of deficient surround inhibition in FHD and PD, it is clear that the surround inhibition abnormality is not the full physiological explanation of dystonia and overflow, and the full functional implications of the abnormality are not yet understood. In PD, the underlying mechanism for the loss of surround inhibition might be different than in FHD. Dopamine depletion in the substantia nigra and the striatum leads to an abnormal increase in tonic inhibition onto the thalamo-cortical output (Mink, 1996). As a result, the appropriate release of the desired motor program in PD patients may require recruitment of more parallel motor circuits in order to compensate this thalamo-cortical deficit. This compensation could lead to interference between competing motor programs and thereby perturb the contrast between them, meaning perturb surround inhibition in the motor system. This idea is supported by evidence that the initiation and completion of a movement in PD patients requires more time for activation (Godaux et al. 1992; Chen et al. 2001), more cycles of agonist–antagonist bursts (Hallett and Khoshbin 1980), and an over-activation of the primary motor cortex (Sabatini et al. 2000).

Therapeutic implications

Surround inhibition is defective in FHD (Sohn et al. 2004b; Beck et al. 2008) and appears to be at least a partial explanation for some of the clinical manifestations. There are number of deficient intracortical inhibitory circuits in FHD and these are partly responsible for the loss of surround inhibition. Drugs that have been proven to have beneficial effects in FHD, such as GABA-ergic drugs like clonazepam, muscle-relaxants like baclofen or anticholinergics like trihexiphenidyl and scopolamine, can increase central nervous system inhibition and may have their beneficial effects by improving surround inhibition. Effects can be evaluated using TMS methods (Ziemann et al. 2004). It would be interesting to study these drug effects in the future both for their effects in normal subjects and in patients with FHD. Whether surround inhibition can be influenced selectively, however, is not clear.

Conclusion

It is clear that surround inhibition is a physiological process in the functioning of the motor system, but the exact mechanism by which it occurs still needs more investigation. Much of the work so far in humans has been conducted with TMS, and there is certainly more that can be done, but this would be a nice area for investigation with non-human primates as well. Surround inhibition breaks down in some movement disorders, and at least in dystonia it seems have some explanatory power for understanding the pathophysiology.

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Literature

Andersen P, Hagan PJ, Phillips CG, Powell TP. Mapping by microstimulation of overlapping projections from area 4 to motor units of the baboon's hand. Proc R Soc Lond B Biol Sci. 1975; 188:31–36. [PubMed: 234617]

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Arm, Reu Neumsci. 1986; 9:357–381.

Angelucci A, Levitt JB, Lund JS. Anatomical origins of the classical receptive field and modulatory surround field of single neurons in macaque visual cortical area V1. Prog Brain Res. 2002; 136:373–388. [PubMed: 12143395]

Baker SN, Olivier E, Lemon RN. An investigation of the intrinsic circuitry of the motor cortex of the monkey using intracortical microstimulation. Exp Brain Res. 1998; 123:397–411. [PubMed: 9870600]

Bara-Jimenez W, Catalan MJ, Hallett M, Gerloff C. Abnormal Somatosensory Homunculus in Dystonia of the Hand. Annals of Neurology. 1998; 44(5):828–830. [PubMed: 9818942]

Beck S, Pirio Richardson S, Shamim EA, Dang N, Schubert M, Hallett M. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. J Neurosci. 2008 Oct 8; 28(41):10363–9. [PubMed: 18842895]

Beck S, Shamim EA, Pirio Richardson S, Schubert M, Hallett M. Interhemispheric inhibition contributes to reduced surround inhibition in dystonia. Eur J Neurosci. 2009a Apr; 29(8):1634–1640. [PubMed: 19419426]

Beck S, Schubert M, Richardson SP, Hallett M. Surround inhibition depends on the force exerted and is abnormal in focal hand dystonia. J Appl Physiol. 2009b Nov; 107(5):1513–8. [PubMed: 19713426]

Beck S, Houdayer E, Pirio Richardson S, Hallett M. Premotor-motor inhibition is increased at rest in patients with focal hand dystonia. Brain Stimulation. 2009c Oct; 2(4):208–214. [PubMed: 20633420]

Beck S, Hallett M. Surround inhibition is modulated by task difficulty. Clin Neurophysiol. 2010 Jan; 121(1):98–103. [PubMed: 19906559]

Blakemore C, Carpenter RH, Georgeson MA. Lateral inhibition between orientation detectors in the human visual system. Nature. 1970; 228:37–39. [PubMed: 5456209]

Chen R, Kumar S, Garg RR, Lang AE. Impairment of motor cortex activation and deactivation in Parkinson's disease. Clin Neurophysiol. 2001; 112:600–7. [PubMed: 11275531]

Collins R. Use of cortical circuits during focal penicillin seizures: An autoradiographic study with [14C]Deoxyglucose. Brain Research. 1978; 150:487–501. [PubMed: 678986]

Conte A, Gilio F, Iezzi E, Frasca V, Inghilleri M, Berardelli A. Attention influences the excitability of cortical motor areas in healthy humans. Exp Brain Res. 2007; 182(1):109–17. [PubMed: 17516055]

Denny-Brown, D. The fundamental organization of motor behavior. In: Yahr, M.; Purpura, D., editors. Neurophysiological basis of normal and abnormal motor activities. New York: Raven; 1967. p. 415-442.

Duque J, Murase N, Celnik P, Hummel F, Harris-Love M, Mazzoccio R, Olivier E, COHEN LG. Intermanual Differences in movement-related interhemispheric inhibition. J Cogn Neurosci. 2007; 19:204–213. [PubMed: 17280510]

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. J Physiol. 1992; 453:525–546. [PubMed: 1464843]

Godaux E, Koulischer D, Jacquy J. Parkinsonian bradykinesia is due to depression in the rate of rise of muscle activity. Ann Neurol. 1992; 31:93–100. [PubMed: 1543354]

Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The basal ganglia and adaptive motor control. Science. 1994; 265:182tL1831. [PubMed: 8023138]

Hallett M, Khoshbin S. A physiological mechanism of bradykinesia. Brain. 1980; 103:301–14. [PubMed: 7397480]

Hallett M. Surround inhibition. Suppl Clin Neurophysiol. 2003; 56:153–159. [PubMed: 14677389]

Hallett M. Dystonia: abnormal movements result from loss of inhibition. Adv Neurol. 2004; 94:1–9. [PubMed: 14509648]

Hallett M. Pathophysiology of writer's cramp. Hum Mov Sci. 2006; 25:454–63. [PubMed: 16859794]

HooverJ E, Strick PL. Multiple output channels in the basal ganglia. Science. 1993; 259:813–21.

Huntley GW, Jones EG. Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. J Neurophysiol. 1991; 66:390–413. [PubMed: 1723093]

Jedynak PC, Tranchant C, de Beyl DZ. Prospective clinical study of writer's cramp. Mov Disord. 2001; 16:494–9. [PubMed: 11391744]

Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in human motor cortex. J Physiol (Lond). 1993; 471:501–519. [PubMed: 8120818]

Landgren S, Phillips CG, Porter R. Cortical fields of origin of the monosynaptic pyramidal pathways to some alpha motoneurones of the baboon's hand and forearm. J Physiol. 1962; 161:112–125. [PubMed: 14461966]

Liepert J, Classen J, Cohen LG, Hallett M. Task-dependent changes of intracortical inhibition. Exp Brain Res. 1998; 118:421–6. [PubMed: 9497149]

Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol. 1996; 50:381–425. [PubMed: 9004351]

Murase N, Duque J, Mazzoccio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol. 2004; 55:400–409. [PubMed: 14991818]

Nauta WJH, Mehler WH. Projections of the Ientiforrn nucleus in the monkey. Brain Res. 1966; 1:3–42. [PubMed: 4956247]

Parent A, De Bellefeuille L. Organization of efferent Projections from the internalsegment of globus pallidus in primate as revealed by a fluorescenceretrograde labelling method. Brain Res. 1982; 245:201–213. [PubMed: 7127069]

Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937; 37:389–443.

Pirio Richardson S, Bliem B, Voller B, Dang N, Hallett M. Long-latency afferent inhibition during phasic finger movement in focal hand dystonia. Exp Brain Res. 2009; 193:173–9. [PubMed: 18936921]

Quartarone A, Rizzo V, Terranova C, Morgante F, Schneider S, Ibrahim N, Girlanda P, Bhatia KP, Rothwell JC. Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia. Brain. 2009 Oct; 132(Pt 10):2871–7. [PubMed: 19690095]

Richardson SP, Bliem B, Lomarev M, Shamim EA, Dang N, Hallett M. Changes in short afferent inhibition during phasic movement in focal dystonia. Muscle Nerve. 2008 Mar; 37(3):358–63. [PubMed: 18061936]

Rouiller EM, Liang F, Babalian A, Moret V, Weisendanger M. Cerebellothalamocortical and palIidothalamocortical projections to the primary and supplementary motor cortical areas: a multiple tracing study in macaque monkeys. J Comp Neurol. 1994; 345:185–213. [PubMed: 7523459]

Sabatini U, Boulanouar K, Fabre N, Martin F, Carel C, Colonnese C, et al. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain. 2000; 123:394–403. [PubMed: 10648446]

Schieber MH. Motor control: basic units of cortical output? Curr Biol. 2004; 14:R353–R354. [PubMed: 15120090]

Schieber MH, Poliakov AV. Partial inactivation of the primary motor cortex hand area: effects on individuated finger movements. J Neurosci. 1998; 18:9038–9054. [PubMed: 9787008]

Schieber MH, Hibbard LS. How somatotopic is the motor cortex hand area? Science. 1993; 261:489–492. [PubMed: 8332915]

Schieber MH. Individuated finger movements of rhesus monkeys: a means of quantifying the independence of the digits. J Neurophysiol. 1991; 65:1381–1391. [PubMed: 1875247]

Shin HW, Sohn YH, Hallett M. Hemispheric asymmetry of surround inhibition in the human motor system. Clinical Neurophysiology. 2009; 120:816–819. [PubMed: 19299196]

Shin HW, Kang SY, Sohn YH. Disturbed surround inhibition in preclinical parkinsonism. Clin Neurophysiol. 2007; 118:2176–2179. [PubMed: 17709287]

Schneider C, Devanne H, Lavoie BA, Capaday C. Neural mechanisms involved in the functional linking of motor cortical points. Exp Brain Res. 2002; 146:86–94. [PubMed: 12192582]

Slobounov S, Johnston J, Chiang H, Ray WJ. Motor-related cortical potentials accompanying enslaving effect in single versus combination of fingers force production tasks. Clin Neurophysiol. 2002; 113:1444–1453. [PubMed: 12169327]

Sohn YH, Hallett M. Disturbed surround inhibition in focal hand dystonia. Ann Neurol. 2004a; 56:595–599. [PubMed: 15455393]

Sohn YH, Hallett M. Surround inhibition in human motor system. Exp Brain Res. 2004b; 158:397–404. [PubMed: 15146307]

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain. 2000 Mar; 123(Pt 3):572–84. [PubMed: 10686179]

Stinear CM, Byblow WD. Impaired modulation of intracortical inhibition in focal hand dystonia. Cereb Cortex. 2004; 14:555–561. [PubMed: 15054071]

Tamburin S, Manganotti P, Marzi CA, Fiaschi A, Zanette G. Abnormal somatotopic arrangement of sensorimotor interactions in dystonic patients. Brain. 2002; 125:2719–2730. [PubMed: 12429599]

Tamburin S, Fiaschi A, Andreoli A, Marani S, Zanette G. Sensorimotor integration to cutaneous afferents in humans: the effect of the size of the receptive field. Exp Brain Res 2005. 2005 Dec; 167(3):362–9.

Tinazzi M, Priori A, Bertolasi L, Frasson E, Mauguiere F, Fiaschi A. Abnormal sensory integration of a dual somatosensory input in dystonia. Brain. 2000; 123:42–50. [PubMed: 10611119]

Zatsiorsky VM, Li ZM, Latash ML. Enslaving effects in multifinger force production. Exp Brain Res. 2000; 131:187–195. [PubMed: 10766271]

Weise D, Schramm A, Stefan K, Wolters A, Reiners K, Naumann M, Classen J. The two sides of associative plasticity in writer's cramp. Brain. 2006; 129:2709–21. [PubMed: 16921180]

Yamamoto T, Hassler R, Huber C, Wagner A, Sasaki K. Electrophysiological studies on the pallido- and cerebelIothalamic projections in the squirrel monkey. Exp Brain Res. 1983; 51:77–87. [PubMed: 6309551]

Zehr EP, Stein RB. Interaction of the Jendrassik maneuver with segmental presynaptic inhibition. Exp Brain Res. 1999; 124:474–480. [PubMed: 10090659]

Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol. 1996 Nov 1; 496(3):873–81. [PubMed: 8930851]

Ziemann U. TMS and drugs. Clinical Neurophsiology. 2004; 115:1717–1729.

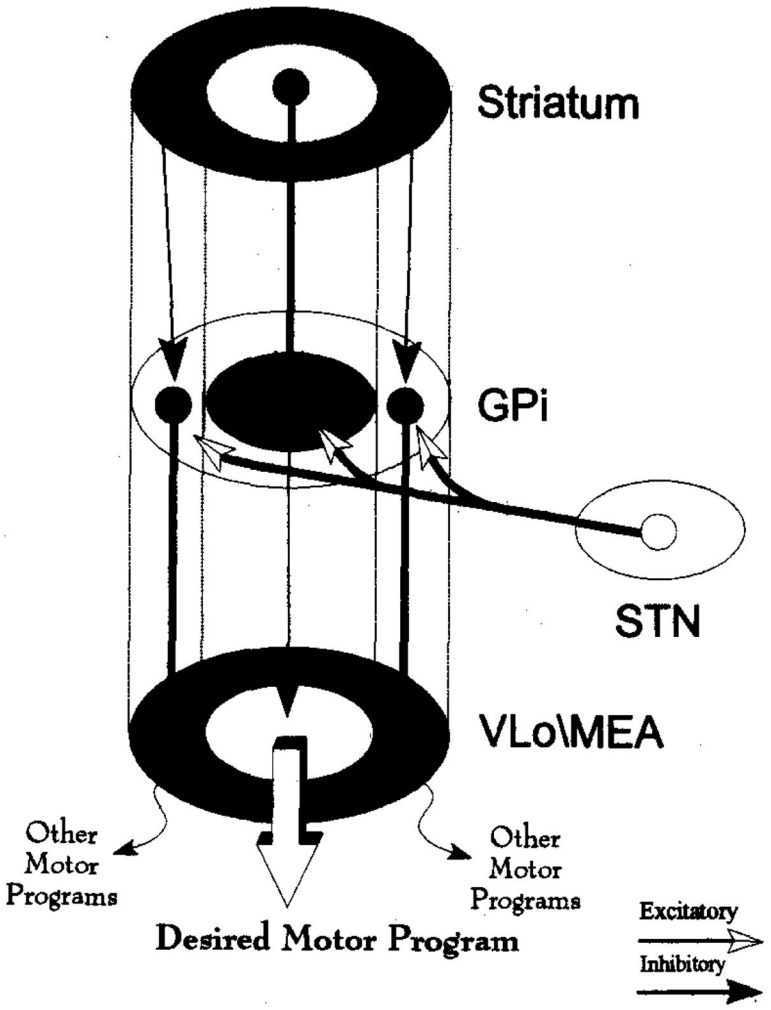

Figure 1.

(from Mink et al. 1996): Relationship of GPi activity to inputs from striatum and subthalamic nucleus. During voluntary movement, excitatory subthalamopallidalneurons increase the activity of the pallidal neurons in the territory surrounding a functional center. Inhibitory striatopallidal neurons inhibit the functional center, resulting in a focused output pattern. The pallidal activity changes are conveyed to the targets in thalamus (VLo) and midbrain (MEA), causing disinhibition of neurons involved in the desired motor program and inhibition of surrounding neurons involved in competing motor programs. Abbreviations — GPi: globus pallidus, pars interna; MEA: midbrain extrapyramidal area; STN: subthalamic nucleus; VLO: ventral lateral thalamic nucleus, pars oralis. Excitatory projections are indicated with open arrows inhibitory projections are indicated with filled arrows. Relative magnitude of activity is represented by line thickness.

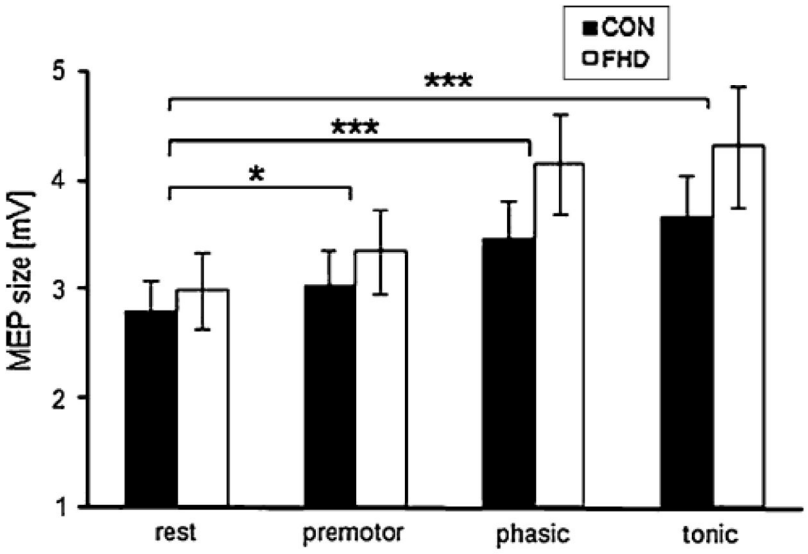

Fig. 2.

(from Beck et al. 2008). MEP size in FDI (Wrst dorsal interosseus muscle, synergist muscle). Shown are the mean MEP sizes with SEs in FDI during movement in both groups (FHD patients and controls) during the four phases. MEP size shows an increase for all active tasks compared with rests underlining the muscle's active role in the selected movement. There was no diVerence in modulation between FHD patients and controls (*P < 0.05, **P < 0.01, ***P < 0.005)

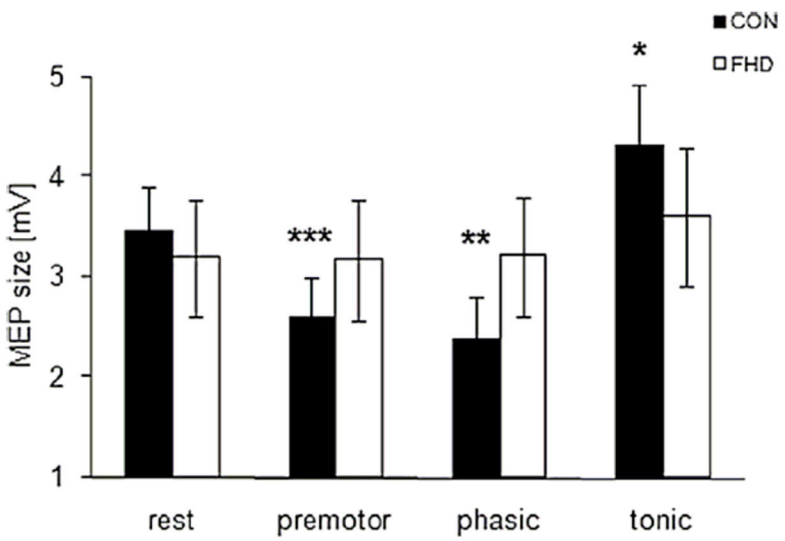

Figure 3. (from Beck et al. 2008)

MEP size in APB (abductor pollicis brevis muscle, surrounding muscle). Shown are the mean MEP sizes with SEs in APB during the FDI (first dorsal interosseus muscle) movement for both groups (FHD patients and controls) during the four phases of the movement. Whereas the MEP size shows a clear inhibition just before and during the first phase of EMG onset in the adjacent muscle (FDI), there is an enhancement during the tonic contraction. Both modulations are not observable in the FHD patient group. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.005$.

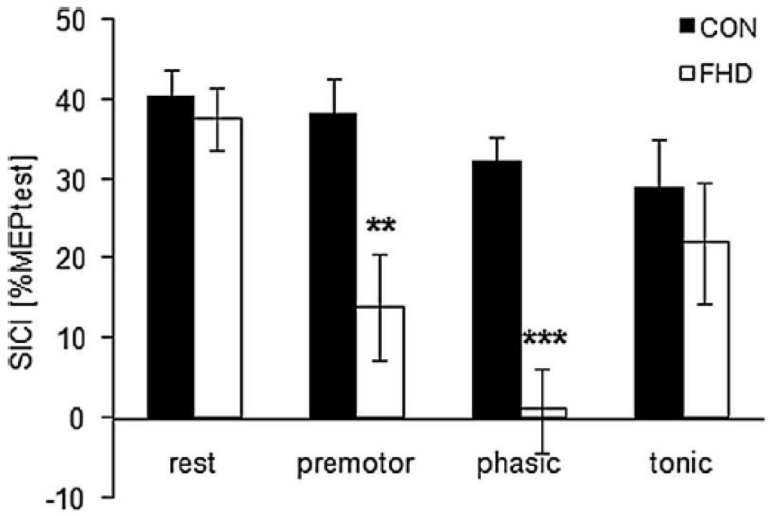

Figure 4. (from Beck et al. 2008)

SICI (short intracortical inhibition) is shown as group mean percentage change [SICI = (MEP test - MEP conditioned/MEP test)*100] with SEs. For the rest condition and tonic state, there is no difference between FHD patients and controls. For patients, SICI is reduced during premotor and phasic phases of the adjacent FDI contraction. In the control group, SICI shows no phase-specific modulation. ** $p \leq 0.01$; *** $p \leq 0.005$.

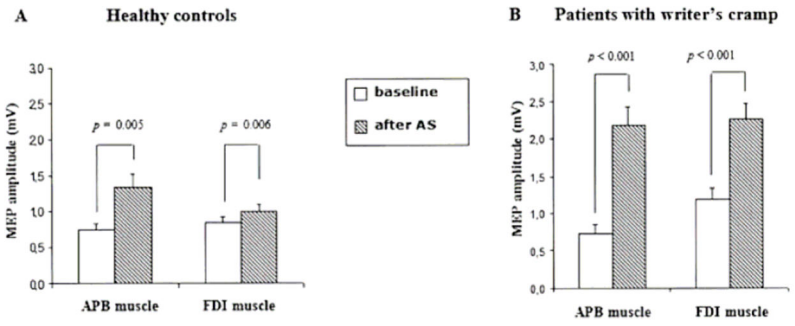

Figure 5. (from Quartarone et al. 2003)

Effect of associative stimulation (AS) on the size of motor evoked potentials (MEPs) of the right APB and FDI muscle in 10 healthy controls (A) and 10 patients with writer's cramp (B). The bar chart illustrate the mean peak-to-peak amplitude (mV) of MEPs recorded at rest before (open columns) and after (shaded columns) associative stimulation. Each error bar equals SEM. Associative stimulation led to an increase in MEP size in patients and controls. However, the facilitatory effect was significantly stronger and less focal in patients.